



Complete Summary

GUIDELINE TITLE

Use of gemcitabine in non-small cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Ellis P, Mackay JA, Evans WK. Use of gemcitabine in non-small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Sep. 29 p. (Practice guideline; no. 7-8). [49 references]

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Non-small cell lung cancer (NSCLC)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations about the use of gemcitabine, alone or in combination, in the treatment of patients with locally advanced or metastatic non-small cell lung cancer

TARGET POPULATION

Adults with locally advanced or metastatic non-small cell lung cancer who are considered candidates for first-line or second-line chemotherapy

INTERVENTIONS AND PRACTICES CONSIDERED

Gemcitabine (Gemzar®) as first-line chemotherapy:

1. Single-agent gemcitabine
2. Gemcitabine combined with cisplatin
3. Gemcitabine combined with carboplatin
4. Platinum-based triplet regimens containing gemcitabine
5. Non-platinum regimens containing gemcitabine

Gemcitabine as second-line chemotherapy:

1. Single-agent gemcitabine
2. Gemcitabine-taxane combinations
3. Gemcitabine-vinorelbine combinations

MAJOR OUTCOMES CONSIDERED

- Survival
- Response rate
- Symptomatic response
- Response duration
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1966 through June 2002), CANCERLIT (1975 through June 2002), and the Cochrane Library (2002, Issue 2) databases were searched for evidence relevant to this practice guideline report. "Carcinoma, non-small cell lung" (Medical subject heading [MeSH]) was combined with each of the following phrases used as text words: "non small cell lung", "gemcitabine" and "gemzar". These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, and

randomized controlled trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (www.cancer.gov/search/clinical_trials) and conference proceedings of the American Society of Clinical Oncology (ASCO, 1998 through 2001) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. The Canadian Medical Association Infobase and the National Guidelines Clearinghouse were searched for existing evidence-based practice guidelines.

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the literature if they met the following criteria:

1. Study conducted in patients with advanced stage non-small cell lung cancer;
2. Randomized clinical trial of gemcitabine as first-line chemotherapy, alone or in combination with other chemotherapy agents, compared to best supportive care (BSC) or another chemotherapy regimen;
3. Randomized or phase II clinical trials of gemcitabine, alone or in combination, as second-line chemotherapy;
4. The trial was fully published or presented in abstract form at ASCO. Abstracts from the ASCO meetings were included in the guideline because most key research findings are first presented at ASCO, which is the largest clinical oncology meeting in the world.
5. Response rate and/or survival data were reported.

Exclusion criteria

1. Letters and editorials;
2. Papers published in a language other than English;
3. Phase II clinical trials published in abstract form only.

NUMBER OF SOURCE DOCUMENTS

Thirty randomized trials were included.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

It was decided not to pool the results of the randomized trials since the combination of chemotherapy regimens used was heterogeneous. As no two studies had the same treatment arms, a meaningful comparison of aggregate data could not be done.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

There was consensus among members of the Lung Disease Site Group (DSG) that there is sufficient evidence from randomized clinical trials to recommend cisplatin-gemcitabine as a first-line treatment option for patients with advanced non-small cell lung cancer (NSCLC). Differences exist in both the toxicity and scheduling of combination regimens, including cisplatin-gemcitabine, and these factors should be considered in deciding which regimens to recommend to an individual patient. An additional consideration of increasing importance in Ontario is timely access to surgical services for the insertion of venous access devices. As this is frequently required in patients receiving vinorelbine, those patients with difficult venous access should be preferentially considered for cisplatin-gemcitabine. In some areas in the province which serve small remote communities, patients may be seen initially at a regional cancer clinic and then have chemotherapy administered under the supervision of their family physician. Gemcitabine may be preferred in these situations because there are fewer concerns regarding extravasation.

There was discussion as to whether the recommendation for the combination of cisplatin-gemcitabine should be restricted to patients in select circumstances or should be available as an option for all patients with advanced NSCLC. The Lung DSG felt that as cisplatin-gemcitabine may have less toxicity than the currently recommended regimen of cisplatin-vinorelbine and there are factors restricting access to the cisplatin-vinorelbine regimen, cisplatin-gemcitabine should be considered a treatment option for all patients with advanced NSCLC.

Two different schedules of cisplatin-gemcitabine have been evaluated in large randomized clinical trials: gemcitabine 1000 mg/m² on days 1, 8, and 15 and cisplatin 80 to 100 mg/m² every four weeks; gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 to 80 mg/m² every three weeks. Following discussions among group members, the Lung DSG chose not to recommend one dose schedule over another, as there are no trials directly comparing these two combinations. However, there appears to be less toxicity with the three-week schedule of treatment, as this schedule contains a lower dose of cisplatin.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 38 practitioners in Ontario (all medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung Cancer Disease Site Group (DSG) reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Seven PGCC members approved the practice guideline report as written and four members approved the guideline and provided suggestions for consideration by the Lung DSG. The Lung DSG reviewed the PGCC suggestions and revised the guideline as deemed appropriate.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Cisplatin-gemcitabine can be recommended as one of several first-line chemotherapy regimen options for patients with locally advanced or metastatic non-small cell lung cancer.
- There is insufficient evidence to recommend adding a third drug to a gemcitabine-platinum combination.
- There is insufficient evidence to recommend routinely substituting carboplatin for cisplatin when combined with gemcitabine.
- At present there is insufficient evidence to recommend gemcitabine combined with a taxane as first-line therapy for non-small cell lung cancer.
- There is currently no evidence from randomized clinical trials that second-line chemotherapy with gemcitabine is associated with any improvement in survival. The routine use of gemcitabine as second-line chemotherapy cannot be recommended.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Of the 30 randomized trials included in this guideline, 14 were reported in abstract form only. For two of these, information reported in the guideline was obtained from both the abstract and the presentation provided on the web site of the American Society of Clinical Oncology.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- There were ten randomized clinical trials of first-line chemotherapy comparing cisplatin-gemcitabine to other chemotherapy regimens, most commonly cisplatin-vinorelbine or a platinum-taxane combination. Response rates for the cisplatin-gemcitabine regimen varied from 22% to 67%, with a range in median survival from 8.1 to 9.8 months. Three large randomized trials, two of which were reported in abstract form only, detected similar response rates and survival for cisplatin-gemcitabine compared with cisplatin-vinorelbine, cisplatin-paclitaxel, carboplatin-paclitaxel, and cisplatin-docetaxel. The cisplatin-gemcitabine combination had a longer time to progression compared with cisplatin-paclitaxel in one study (4.2 versus 3.4 months, $p=0.001$) but this was not associated with any improvement in median survival (8.1 versus 7.8 months), or one-year survival (36% versus 31%).
- There were seven randomized trials of three drug regimens containing gemcitabine as first-line chemotherapy. Three trials by the Southern Italian Cooperative Oncology Group, which may include some of the same data, detected improved response rates and survival for cisplatin with gemcitabine and either vinorelbine or paclitaxel compared with two drug combinations. Three additional large randomized trials published in abstract form showed no benefit from three drug combinations compared to two drug combinations. One small randomized trial, also published in abstract form, detected a higher response rate for a triplet regimen of gemcitabine-carboplatin-paclitaxel compared to a doublet regimen of carboplatin-paclitaxel (61% versus 28%, $p=0.017$).
- Thirteen phase II trials of gemcitabine alone or in combination as second-line chemotherapy showed response rates of 3% to 33% and a median survival of 3.9 to 11 months.

POTENTIAL HARMS

There were differences in the toxicity of cisplatin-gemcitabine in comparison with other regimens. Grade 3/4 thrombocytopenia and anemia generally occurred more often with cisplatin-gemcitabine. The difference was reported as significant for thrombocytopenia when compared with cisplatin-etoposide (55% versus 13%, $p=0.0457$), mitomycin-ifosfamide-cisplatin (38% versus 12%, $p<0.001$), cisplatin-vinorelbine (16% versus <1%, $p<0.05$), and cisplatin-paclitaxel (50% versus 6%, $p<0.05$) and for anemia when compared with cisplatin-paclitaxel (28% versus 13%, $p<0.05$). The frequency of neutropenia was more variable although it was more common with cisplatin-etoposide (76% versus 64%, $p=0.0009$) and cisplatin-vinorelbine (44% versus 16%, $p<0.05$) than with cisplatin-gemcitabine.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Other first-line chemotherapeutic options that have shown response rates and survival outcomes equivalent to the combination of cisplatin-gemcitabine include (i) cisplatin-vinorelbine, (ii) carboplatin-paclitaxel, (iii) cisplatin-paclitaxel, and (iv) cisplatin-docetaxel.
- Differences in scheduling and toxicity of these regimens should be the criteria used to choose between the different therapies.
- Preliminary evaluations of two different dose schedules of cisplatin-gemcitabine have been conducted in large randomized clinical trials: gemcitabine 1000 mg/m² on days 1, 8, and 15 and cisplatin 80 to 100 mg/m² every four weeks; gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 to 80 mg/m² every three weeks. There is insufficient evidence to recommend a specific schedule at this time.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lung Cancer Disease Site Group. Ellis P, Mackay JA, Evans WK. Use of gemcitabine in non-small cell lung cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Sep. 29 p. (Practice guideline; no. 7-8). [49 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 Oct 14 (revised 2002 Sep)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Lung Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members of the Lung Cancer Disease Site Group, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Lung Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Use of gemcitabine in non-small cell lung cancer. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 17, 2001 and most recently on June 23, 2003. The most recently updated information was verified by the guideline developer as of July 16, 2003.

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